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THE ROLE OF CYP2E1 POLYMORPHISM IN THE ACTIVATION OF PROCARCINOGEN METABOLISM OF NASOPHARYNGEAL CARCINOMA

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Abstract

Intoduction: Cytochrome P450 2E1 (CYP2E1) is the enzyme as a part of CYP 450 enzyme families. It acts in phase I metabolism which result in the formation of electrophilic molecule and elevation of reactive oxygen species (ROS).
Discussion: ROS is formed by the metabolism reaction of CYP2E1. This molecules is responsible in development of cancer by damaging the protein and DNA, leading to mutation and increase cell proliferation. Nitrosamine as the most carcinogen for nasopharyngeal carcinoma (NPC) is the substrate of this enzyme. This chemical is contained in the salted fish, tobacco smoke, beer, and preserved food such as meat product.
Conclusion: Nitrosamine needs CYP2E1 to activate the pro-carcinogen in order to act its carcinogenic effect. Polymorphism of CYP2E1 is associated with higher transcriptional activity and enzyme activity. Therefore, the ability of CYP2E1 to activate pro-carcinogen of nitrosamine will be increased, leading to higher chance to develop cancer, including NPC.

Article Info

Keywords:
Nasopharyngeal carcinoma, CYP2E1, carcinogen, nitrosamine, polymorphism

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1. INTRODUCTION

Cytochrome P450 2E1 (CYP2E1) is member of CYP 450 superfamily [1, 2]. CYP2E1 is expressed and acts its role in the liver [3]. This enzyme had function in metabolism of drugs and chemical substances [4, 5]. It has responsibility in pro-carcinogens activation of several cancer. Nitrosamines as the chemical carcinogens have been found in meat, tobacco smoke and food color additives and the pro-carcinogens of this compound is activated by CYP2E1[6, 7]. CYP2E1 activates this xenobiotics into toxic substances and the induction is the first step in chemical induced carcinogens [8].

Nasopharyngeal carcinoma (NPC) is malignancies which rare in the world but common in Southern China and Southeast Asia [9]. In Indonesia, this cancer is frequent and the overall incidence of NPC estimated at 6.2/100 000 or about 12 000 new cases per year [10]. NPC is developed by the association of genetic abnormalities, Epstein Barr Virus (EBV) infection and the environmental factor such as consumption of salted fish, smoked fish/meat, smoking, and alcohol consumption [11, 12]. Alteration of genes responsible in immune regulation, carcinogens metabolism, DNA damage and repair also tumorigenesis were known associated with NPC [13]. Polymorphism of CYP2E1 as enzyme acts in metabolism of carcinogens is a risk factor for NPC.

Several studies have found the polymorphism of CYP2E1 in cancers including gastrointestinal cancer, breast cancer, lung cancer and also head and neck cancer[14-16]. Polymorphism of the gene which is the homozygote variant type (T allele/c2c2/(-/-)) is associated with higher transcription and activity of CYP2E1 than the wild type (c1/c1/(+/+)) [17, 18]. Nitrosamine is contained in salted preserved food and tobacco as the environmental risk factor of NPC [19]. The polymorphism of CYP2E1 might be increase the activity of the enzyme to activate pro-carcinogens leading to the development of NPC.

2. MAIN TEXT

2.1 Carcinogen in NPC

NPC can be induced by the environmental factors including dietary factors, tobacco and alcohol intake [20]. Those factors is associated in the development of NPC due to carcinogens which is contained in them. Carcinogens is the chemical substances causing cancer [21]. Generally, carcinogens is divided by genotoxic type and non-genotoxic type as well as its mechanism in initiating cancer, genotoxic and non-genotoxic mechanism [22, 23]. Most of the causes is genotoxic carcinogens with its effect in triggering DNA mutation or chromosomal aberration. This substances interfere cell progression, proliferation, differentiation, DNA replication and repair and also in apoptotic pathways. Carcinogens regulate cell cycle by acceleration or arrest cell cycle progression including induce cell cycle arrest in G1 phase, increase G1 phase, activating cell cycle checkpoints due to DNA damage formation and also enhance cells to enter into S phase which one of the causes is nitrosamine [22, 24]. Non-genotoxic carcinogens accounts for 10-20% carcinogens and works in carcinogenesis by altering epigenetics, endocrine system, apoptotic signaling, cell proliferation and/or gap-junctional intercellular communication [23].

Above, we stated that carcinogens can be genotoxic and non-genotoxic with genotoxic is more dominant induce cancer. These genotoxic substance include microcystins-LR (MCLR), polycyclic aromatic hydrocarbons, aromatic amines, N-nitrosamines, aflatoxins, and benzene, 2-Amino-3-methylimidazo [4,5-f]quinoline (IQ), aflatoxin B1 (AFB1), benzo[a]pyrene (BaP) and cisplatin (CisPl) and many others [22, 25]. N-nitrosamines is the carcinogens which can be found in air, water, foods, cosmetics, tobacco and packing materials [26]. This is one of the carcinogen responsible in enhancing NPC.

There was several study which showed the association of N-nitrosamine with cancer. It was showed that nitrosamine induced bladder cancer [27]. Other study presented that nitrosamine such as nicotine-derived nitrosamine ketone (NNK) can induce formation of radical oxygen species and leading to lung cancer [28]. N-Dinitrosopiperazine also had been known can induce nasopharyngeal carcinoma and also its metastasis [29].

In food such as meat, salted fish, beer and water, N-nitrosamines are the result of the reaction between organic amine or secondary amine and their derivatives with the nitrosating compounds such as nitrogen oxide or nitrite. Nitrite is mostly used as preservation of meat products. In beer, water and also food, N-nitrosodimethylamine (NDMA) is the common type of N-nitrosamine which has been found. The method of cooking also affect the content of nitrosamines in it. Food which was fried and baked contains higher N-nitrosamine than the raw one. The temperature of 990C-1850C was effective to increase N-nitrosamine formation [26, 30].

In the tobacco, nitrite is formed by microbe on or in the plant before, during and after curing. The reaction between nitrite as the predominant nitrogen oxide with nicotine produces tobacco specific nitrosamines (TSNAs) [31]. Types of TSNAs with the most carcinogenic effect are NNK and N-nitrosonornicotine (NNN) [32]. However, besides TSNAs, there is another carcinogen in person who smokes tobacco, tar. Tar is genotoxic substance in tobacco smoke. It is composed of carcinogenic compounds such as benzopyrene, dibenzanthracene, and other polyaromatic hydrocarbons which cause free radical formation [33].

2.2 Metabolism of genotoxic carcinogen and CYP2E1

Metabolism is the process of change of chemicals from one part of chemicals to another by enzyme. The aim of metabolism is for detoxification by excreting endogenous and/or exogenous molecules from the body. It converts lipophilic chemicals to hydrophilic one so that it can eliminated from the body [34, 35]. Metabolism mostly consists two-step process, phase I and phase II. Phase I is the process of oxidoreductions and hydrolysis, showing nucleophilic groups [36]. Phase I metabolism can produce the products which is reactive intermediates and more toxic by bioactivation [35]. This phase is through the cytochrome P450 (CYP450) enzymes activity. However, phase II is the process which is conjugation of nucleophilic groups with endogenous molecule including glucuronic acid or glutathione so it can be more hydrophilic and less toxin and then excreted from the body. It works by the activity of Glutathione S- Transferase (GST), NAD(P)H: Quinone oxidoreductase (NOO), Cytosolic sulfotransferases (SULT), Epoxide hydrolase (EPHX), UDP-Glucuronosyl transferase (UGT), Methyltransferase (MT), N-Acetyltransferase (NAT) [34, 37].

Genotoxic carcinogen is needed to underwent metabolism in order to activate the carcinogen effect [22]. Most this carcinogens are pro-carcinogens which need activation to form the electrophilic substance and perform the genotoxic effect [38]. As we have said before, the activation of chemicals to nucleophilic group is done by CYP450 enzymes group in the phase I metabolism. This enzyme is involved in the activation of potential pro-carcinogens [39]. The enzymes activity requires oxygen activation, leading to reactive oxygen species (ROS) formation including superoxide anion (O2), hydrogen peroxide (H2O2), and hydroxyl radical (OH). ROS are harmful to the cells due to their action to denature proteins, inactivate enzymes and cause RNA and DNA damage [40].

CYP2E1 is part of CYP enzymes which is involved in metabolic activation of more than 85 xenobiotics to become hepatotoxic and carcinogenic. This enzyme is distributed in liver, kidneys, nasal mucosa, brain and lungs [41]. The gene is located on chromosome 10q26.3. It has role in the bioactivation of ethanol, acetone, benzene, N-nitrosamine and vinyl chloride [42]. CYP2E1 has great ability in generating ROS due to uncoupling of oxygen consumption with NADPH oxidation. It is supported by its high level of expression in mitochondria. The oxidative stress which signed by the elevation of ROS is responsible in the development of cancer [43]. It causes the damage of protein, DNA, and/or lipid, result in chromosome instability, genetic mutation, and/or enhancing of cell growth [44].

Nitrosamine can induced the cancer by activation of CYP2E1 enzyme. Gao at al. in their study found the effect of CYP2E1 activity for the pro-carcinogen activation of diethylnitrosamine (DEN) as the most common nitrosamine. It showed by the increase of hepatofibrosis along with higher CYP2E1 activity. This was supported by decrease of fibrosis with CYP2E1 inhibitors used. Pro-carcinogen of nitrosamine as the substrate for CYP2E1 is enhanced after the induction of CYP2E1 and it is reduced by inhibitors of CYP2E1[6]. Nitrosamine need metabolic activation by CYP2E1 activity to show its carcinogen effect which is increase the intracellular ROS levels [45]. As we have said above, ROS is responsible for carcinogenesis due to its act in damaging DNA and protein.

2.3 Polymorphism of CYP2E1 in NPC

Polymorphism of CYP2E1 has known to be associated with several cancer. The polymorphism of this enzyme is related with higher activity of CYP2E1. Genetic variance of this gene is more than 160 missense and the T allele which is the substitution of a thymine instead of cytosine in wild type allele of CYP2E1 (rs2031920) has the ability in increasing transcriptional activity[46]. The minor T allele is one of polymorphism of CYP2E1 which has been known to has higher transcriptional activity and enzyme activity than the major allele or C allele [18].

However, CYP2E1*5B PstI (rs3813867) is polymorphism of CYP2E1 which is the result of substitution of cytosine instead of guanine in the 1259 position of wild type allele of CYP2E1. The heterozygous c1/c2 and homozygous mutant c2/c2 genotyped has decrease of enzyme activity. CYP2E1*6 DraI (rs6413432) is polymorphism with the substitution of adenine instead of thymine in 7678 position of wild type allele of CYP2E1. CC homozygous mutant of this enzyme is associated with higher enzyme activity [16].

It was showed that polymorphism of CYP2E1 which is CYP2E1*D were significantly associated with oral caners. It was related with the risk factor of oral cancer, tobacco and alcohol consumption which contains carcinogen including nitrosamine and polycyclic aromatic hydrocarbons [47]. Karakoc et al., found that the heterozygous mutant of CYP2E1-RsaI (rs2031920) polymorphism had higher risk for head and cancer susceptibility [16]. Anuradha et al., also found the association of CYP2E1 polymorphism with the increase risk of head and neck cancer. The risk is increases if CYP2E1 act in tobacco carcinogens metabolism [48].

For NPC, it was showed that subjects with homozygous variant genotype had higher risk for NPC, 2.2 fold than subjects with wild type and heterozygous genotype. They also found that the risk was higher in the subjects who smoking, 3.3 fold than nonsmokers [49]. This study showed the effect of CYP2E1 which increased by smoking. It supports the evidence that CYP2E1 has role in NPC development by activating pro-carcinogens, such as nitrosamine which is contained in tobacco smoke. Another study showed the increase risk for NPC in individual with CYP2E1 polymorphism. There were five of ten single-nucleotide polymorphisms (SNPs) including rs9418990, rs915908, rs8192780, rs1536826, rs3827688 were associated with increased risk of NPC [50].

3. CONCLUSION

Development of NPC is multifactorial process by genetic, environmental, and EBV infection. Polymorphism of CYP2E1 is one of genetic involvement for NPC due to alteration of the enzyme and transcriptional activity. CYP2E1 act in phase I metabolism which result in formation electrophilic molecule and ROS generation. The most carcinogen of NPC is nitrosamines which is contained in tobacco smoke, salted fish and preserved food and this chemicals need activation of their pro-carcinogens by CYP2E1 to show their carcinogens effect. Polymorphism of CYP2E1 is associated with the increase of pro-carcinogens activation leading to development of NPC.

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